REMARKS

Status of the Claims

Claims 1-19 are pending. Claims 2, 3, and 7-12 have been withdrawn from further consideration by the Examiner as being directed to a non-elected invention. Claims 1, 4, 6, and 13-19 are currently under consideration. Claim 4 has been amended herein to more particularly point out the invention. Support for the amendment is found in the specification on page 10, lines 4-7, page 13, lines 19-28.

Indefiniteness Rejection Under 35 U.S.C. § 112

Claim 4 stands rejected under 35 U.S.C. § 112 second paragraph as allegedly indefinite. The Office alleges that the claim is rendered indefinite because it is unclear whether the term "one" refers to either the combination of a recombinantly produced α-galactosidase A and an exogenously produced natural α-galactosidase A, or alternatively, to each enzyme individually. Without acquiescing in the rejection, and for the sole purpose of expediting prosecution, Applicants have amended claim 4 to recite: "one of the following: an exogenously produced natural α-galactosidase A, a recombinant α-galactosidase A and a small molecule." Applicants believe the amendment obviates the rejection.

The Rejections Under 35 U.S.C. § 103(a)

Claims 1, 4, 6 and 13-19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Schiffmann et al., 2000, *Proc. Natl. Acad. Sci. USA,* 97:365 (Schiffmann), or Desnick et al., 1979, *Proc. Natl. Acad. Sci. USA,* 76:5326 (Desnick), in

view of Ziegler et al., 1999, *Human Gene Therapy* 10:1667 (Ziegler). The Office alleges that Schiffmann teaches infusing 10 Fabry patients with α-galactosidase A resulting in significantly reduced globotriaosylceramide levels in 9 of the patients. The Office also alleges that Desnick teaches administering α-galactosidase A isozyme to 2 Fabry patients decreased the concentration of globotriaosylceramide 50-70%. The Office further alleges that Ziegler teaches preparation of an adenoviral vector encoding α-galactosidase A, administering the vector to a murine model of Fabry disease and obtaining increased α-galactosidase A expression and a concomitant reduction in globotriaosylceramide. The Office thus concludes that the claimed invention is obvious. Applicants respectfully submit that this conclusion is flawed for the following reasons.

The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine what the reference teaches. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not the Applicant's disclosure. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (emphasis added). The references must be considered as a whole and must suggest the desireability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.,* 229 U.S.P.Q. 182, 187 n.5

(Fed. Cir. 1986) (emphasis added); MPEP § 2141. The Patent and Trademark Office bears the burden of initially establishing a prima facie case of obviousness. MPEP § 2142. The Office has not met its burden in this case.

No Motivation Existed To Combine The References

Nothing in either Schiffmann, Desnick, or Zeigler would motivate a skilled artisan to combine enzyme replacement therapy with gene therapy because a skilled artisan reading Ziegler would conclude gene therapy presented a long term therapy for treating Fabry disease, while in contrast, the beneficial effects of the enzyme replacement therapy suggested by both Desnick and Schiffmann were short lived.

Ziegler obtained significant reduction in globotriaosylceramide ("in all tissues to near normal levels') (Abstract) by administering an adenoviral vector to the Fabry mouse. These reductions were maintained for up to 6 months. While globotriaosylceramide levels began to reaccumulate, Ziegler showed that this problem could be solved by re-administering the vector with an immunosuppresant (i.e., a monoclonal antibody to CD40). Commenting on their results, Ziegler states: "Together these data demonstrate that the defects in α-galactosidase A activity and lysosomal storage of GL-3 in Fabry mice can be corrected by adenovirus-mediated gene therapy. This suggests that gene replacement therapy represents a viable approach for the treatment of Fabry disease . . . " (Abstract) (emphasis added). While Ziegler does comment on the limitations associated with adenoviral gene therapy, they also note that solutions to each of the alleged limitations is readily available. These solutions include administration of immunosuppresants, patient tolerization with adenoviral proteins, and vector modification to remove or inactivate the E2a and E4 viral genes.

In contrast Schiffman discloses a half life of infused α-galactosidase A of 42-117 minutes (page 368, first column) and more importantly, plasma globotriaosylceramide levels were not significantly reduced compared to baseline one week after treatment (page 368 2nd column). While reduction of globotriaosylceramide in liver and urine was observed (an average of 30% and 38% reduction respectively), the data only suggests effect lasted 28 days, compared to the 6 months observed for gene therapy. Moreover, this benefit was not observed in all patients.

The results reported by Desnick were even less impressive. Using the plasma isozyme, which according to Desnick, was superior to the splenic isozyme, globotriaosylceramide levels were reduced 50-70% in 2-6 hours, but rebounded to preinfusion levels in 36-72 hours. Thus, Applicants submit the skilled artisan would conclude after reading the cited references that gene therapy provided a long term solution to the problem of treating Fabry disease, while enzyme replacement therapy provided only marginal short term results.

Applicants urge the Examiner to consider that the requirement regarding the motivation to combine references has been further clarified in *Winner Int'l Royalty Corp. v. Wang,* 53 U.S.P.Q.2d 1581 (Fed. Cir. 2000.) In *Winner,* the Federal Circuit upheld the district court's determination that the claims at issue were not obvious over two prior art references. *Id.* at 1590. The Court has agreed that there was no motivation to combine these references to arrive at the claimed invention because, in part, "there was no apparent disadvantage to the dead-bolt mechanism of [ref 1], and therefore the motivation to combine would not stem from the 'nature of the problem' facing one or ordinary skill in the art, because no 'problem' was perceived." *Id.* at 1587.

Similarly, in making its rejection of the claimed invention, the Office has not identified any apparent disadvantage of, or problem with, the disclosure of Ziegler which would have motivated one to combine its teachings with those of Schiffmann or Desnick.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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